Original Article

Impact of HIV Infection on Radiographic Features in Patients with Pulmonary Tuberculosis

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ABSTRACT

Background. There is insufficient data on the radiographic presentation of tuberculosis in human immunodeficiency virus (HIV) infected patients from India.

Methods. We examined the chest radiographs of 181 patients including 82 HIV positives with newly diagnosed sputum culture positive pulmonary tuberculosis before and after the completion of anti-tuberculosis treatment (ATT). Patients with smear / culture positive pulmonary tuberculosis were treated with Revised National Tuberculosis Control Programme (RNTCP) Cat-I regimen ($2EHRZ_3/4HR_3$). An independent assessor blinded to HIV and clinical status of patients read the radiographs.

Results. At presentation, HIV seropositive patients were significantly more likely to have normal chest radiographs (14.2% *vs* 0), miliary tuberculosis (10.7% *vs* 1%) and pleural effusion (16.6% vs 3%), and less likely to have cavitation (17.8% *vs* 39.4%) as compared to HIV negative patients. At the end of treatment, HIV positive patients were more likely to have normal radiographs (42.8% *vs* 1.2%), and less likely to have fibrosis (17.8% *vs* 42.5%).

Conclusions. The radiographic presentation of pulmonary tuberculosis in HIV-infected patients is atypical with less cavitation, and more dissemination. On completion of ATT, patients with HIV have less radiographic sequelae in the form of fibrosis. These features may be due to the reduced inflammatory response that patients with HIV infection may be able to mount. **[Indian J Chest Dis Allied Sci 2007; 49: 133-136]**

Key words: HIV/ AIDS, Tuberculosis, Chest radiography.

INTRODUCTION

Among factors contributing to the increased incidence of tuberculosis (TB) worldwide, HIV is one of the most important. Since control of tuberculosis in an individual depends on an intact cellular immune response, it is not surprising that HIV infection is a major risk factor for tuberculosis progressing from latent infection to clinical disease. In India, tuberculosis is the most common opportunistic infection among HIV seropositive patients.[1] Patients with HIV co-infection may not have typical radiographic features of pulmonary tuberculsosis. Several studies from Africa, Europe, and South America have reported differences in radiographic manifestations of TB between HIV seropositive and seronegative groups.[2,3,4-10] A few studies have been conducted in India comparing the radiographic features of pulmonary tuberculosis between HIV seropositive and negative individuals.[11,12] We compared pre- and post-treatment radiological features of tuberculosis in these two groups of patients to bring out any radiological outcomes.

MATERIAL AND METHODS

Patients referred to the Tuberculosis Research Center Clinics in Chennai and Madurai between July 1999 and June 2002, and recruited into ongoing clinical trials of the center were included in this analysis. Patients with symptoms suggestive of pulmonary tuberculosis were investigated further. Three sputum specimens were collected for smear microscopy for acid-fast bacilli (AFB) and mycobacterial culture. Human immunodeficiency virus testing was done after pretest counseling and written informed consent. The diagnosis of HIV infection was based on three positive tests (Tridot, J. Mitra and Comb ADIS, Span Diagnostics) followed by an ELISA (Lab System, U.K.). A posteroanterior chest radiograph was done. The diagnosis of tuberculosis was based on sputum smear and culture results along with

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clinical and radiographic features. The CD4 count was done for all HIV positive patients by flow cytometry. Patients with long term steroid therapy, diabetes, and other causes of immunosuppresion were excluded from the study. Based on HIV status, the patients were divided into two groups—positives and negatives.

Patients confirmed to have pulmonary tuberculosis were treated with standard short-course intermittent regimen with two months of ethambutol (1200 mg), INH (600 mg), rifampicin (450/600 mg) based on body weight < 60 kg: 450 mg and > 60 kg: 600 mg] pyrazinamide (1500 mg) given three times a week followed by four months of INH (600 mg) and rifampicin (450/600mg) given thrice weekly. Treatment was supervised completely in the initial intensive phase and once a week in the continuation phase.

The patients were followed up every month with a clinical examination and three sputum examinations. A chest radiograph was repeated at the end of treatment. An independent assessor (NMS) who did not know the clinical background of the patient including HIV status, CD4 and sputum smear status read all the chest radiographs. All patients included in this analysis had *Mycobacterium tuberculosis* isolated from at least one pre-treatment sputum culture specimen and were smear and culture negative at the end of treatment.

Statistical Analysis

Data was entered into excel and analysis was done using SPSS software version 13. All tests were two-tailed and evaluated at a significance level of 0.05. Qualitative variables were expressed as percentage and were compared using the Chi-square test. Continuous variables were expressed as median and were compared using Mann-Whitney test.

RESULTS

One hundred and eighty one patients who had culture confirmed tuberculosis were included in the study out of which 82 were HIV positive. Table 1 shows the demographic characteristics of the study population. The sex distribution was similar in both the groups of patients. The CD4 count was available for 71 HIV positive patients. The median CD4 count was 112 cells/mm^3 ((Interquartile range 42-252). Sixty percent of patients with HIV-TB had sputum smears positive for AFB but all of them were culture positive.

Table 1. Demographic characteristics of study population

	TB+ HIV– (n=99)	TB+ HIV+ (n=82)
Sex	Number (%)	Number(%)
Male	84 (85)	71 (84)
Female	15 (15)	11 (16)
Age		
< 30 years	45 (45)	28 (34)
31-50	38 (38)	51 (62)
> 50 years	16 (16)	3 (4)
Smear Positivity	99 (100)	49 (60)

Table 2 shows the initial radiographic features of patients in the two groups. Some patients had more than one abnormality. Diffuse pulmonary infiltrates/opacities was the most common radiological presentation in both the groups. Cavitation was more common in the HIV negatives pulmonary tuberculosis patients than in those with HIV co-infection. On the other hand, miliary pattern was more common in HIV positive patients. Radiographs were normal in 14.2% of HIV infected patients but in none of the seronegative patients with pulmonary tuberculosis.

Table 2. Radiographic lesions at the time of diagnosis

Type of Lesion	TB+ (n=99) Number (%)	TB+ HIV+ (n=82) Number (%)
Normal*	0	12 (14)
Diffuse infiltrate/opacities*	90 (91)	53 (65)
Cavity*	39 (39)	15 (18)
Pleural effusion*	3 (3)	14 (17)
Miliary TB*	1 (1)	9 (11)
Hilar/Mediastinal lymph nodes	3 (3)	8 (10)
Others	7 (8)	8 (10)

*=<0.01

Radiographs at the end of therapy were evaluated in 80 TB and 82 HIV-TB positive patients. Fibrosis was more often seen in HIV negative TB patients (42.5% *vs* 17.8%). Cavities persisted in 15% of HIV negative TB patients and 8.7% of HIV positive patients. Over all, more HIV patients had a normal chest radiograph at the end of treatment as compared to HIV negative patients (42.8% *vs* 1.2%; p<0.05), table 3.

Table 3. Radiographic lesions at the end of treatment

Type of Lesion	TB+ HIV– (n=80)	TB+ HIV+ (n=82)
Normal**	1 (1)	36 (43)
Diffuse infiltrate/opacities**	62 (76)	27 (32)
Cavity	12 (15)	6 (9)
Fibrosis*	34 (43)	15 (18)
Calcification	1 (1)	0
Hilar nodes	3 (4)	8 (10)
Pleural effusion or thickening	3 (4)	1 (1)
Miliary TB	1 (1)	2 (2)

*=p<0.05, **=<0.01

The number of radiographic zones involved was less in HIV positives compared to HIV negative TB patients both at the beginning (67% *vs* 34% with < 3 zones involved, p<0.05) and the end of treatment (87% *vs* 52.5% with < 3 zones involved, p < 0.05). Among HIV-positive patients, the median CD4 count in patients without cavitation was 87 (IQR 40 to 161) whereas in those with cavity, it was 252 (IQR 160 to 468) (p<0.01).

Table 4. Comparison of radiographic features in HIV positive and negative TB patients reported in series from different countries

Radiological Patterns	Brazil		Rwanda		Zimbabwe		Tanzania		Uganda		Present Study	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Opacities / Infiltrates	66	80	16	55	-	-	84	75	46	26	65	91
Lymphadenopathy	10	3	31	0	26	15	22	6	26	06	10	3
Pleural effusion	15	8	43	9	26	13	31	32	23	11	17	3
Cavitation	18	50	39	91	40	64	23	40	18	57	18	39
Miliary	8	2	-	-	-	-	-	-	7	0	11	1
Normal	8	6	-	-	-	-	-	-			14	0

Note=All values are in percentages

Of the 82 patients with HIV-TB, 46 (56%) had sputum smear graded as negative or 1 + and 36 (44%) of them had a smear of 2 or 3 + grading, while of the 99 TB patients 80 had smears graded as 2 + or 3 + (80%). Sixty percent of the patients with CD4 counts of less than 200 cells / mm^3 had zero or 1 + smear, whereas in patients with CD4 counts of more than 200 cells / mm^3, it was 30 percent. However, there was no significant difference between the median CD4 counts of patients with zero and 1 +, or 2 + and 3 + smear grading.

Table 4 is a comparative chart showing the prevalence of different radiographic features in HIV positive and negative TB patients, in reports from different countries, mostly from Africa.

DISCUSSION

Infection with HIV has now emerged as the most strongest risk factor for the development of active tuberculosis.[1] With the increasing prevalence of HIV infection in India, physicians need to be aware of the different manifestations of tuberculosis in HIV positive patients. This study highlights the fact that radiographic features of tuberculosis are significantly different in HIV infected patients compared to those who are negatives. Tuberculosis can mimic many diseases and *vice-versa*. In HIV-infected individuals the radiographic manifestations of pulmonary tuberculosis can be atypical or different and the diagnosis requires a high index of suspicion.[2, 3]

Our study compared radiographic findings at baseline and at the end of anti-tuberculosis therapy in HIV positive and HIV negative patients with tuberculosis. The commonest radiographic presentations among HIV patients were diffuse soft parenchymal opacities followed by cavities, pleural effusion, miliary tuberculosis and hilar adenopathy. A normal radiograph was also more commonly seen in the patients, in comparison to none in the HIV negative patients. Cavities were more frequent among tuberculosis patients without HIV infection. The higher occurence of cavities, opacities, and fibrosis after treatment in HIV-negative patients may be related to the stronger inflammatory response mounted by these individuals. Those HIV patients who had a cavity had a relatively higher median CD4 than those who did not have cavitation. In a study by Tripathy *et al*, presence of cavitation was related to higher CD4 counts, indicating that a robust immune response is required for cavitation to occur.[13] Further, extra-pulmonary tuberculosis by itself was not associated with decreased CD4 but patients with a combination of pulmonary and extra-pulmonary tuberculosis had significantly lower CD4 counts.[6] Features of dissemination including miliary, mediastinal adenopathy did not show a relationship with CD4 counts possibly due to the small number of patients in this study. There was also no relationship between the grade of sputum smear positivity and the radiographic findings. A unique feature of our study was the comparison of the pre- and post- treatment radiographs, not previously described. The post-treatment radiographic appearances showed that 42.8% had returned to normal in the doubly infected group compared to only 1.2% in the pulmonary tuberculosis group.

The fewer radiographic zones involved initially as well as the higher frequency of normal radiographs, at the end of treatment, indicate the poor cellular inflammatory response and fibrosis mounted by HIV positive persons. It is also known that the tissues are teeming with mycobacteria in HIV positive patients, even though sputum specimen may be smear negative.[7] Examination of bronchoalveolar lavage from involved lung segments in such patients reveals a failure of recruitment and activation of CD4+ lymphocytes (impaired CD4 alveolitis) compared to pulmonary tuberculosis patients seronegative for HIV. This may explain the paucity of consolidation and opacities seen. A number of HIV induced defects in granuloma assembly and function including impaired chemotaxis and proliferation of IFN-γ secreting clones and decreased bactericidal activity of macrophages resulting in reduced granuloma formation, caeseation and liquefaction which preceede cavitation. Failure of containment and early and widespread dissemination may explain the increased prevalence of miliary tuberculosis in HIV patients.[14]

An earlier study from south India showed that cavitatory form of pulmonary tuberculosis was seen in 8% of HIV patients and the miliary in 5 percent.[11] Studies by Debnath *et al*[12] showed that effusion (20% *vs*

10%) and miliary pattern (20% *vs* 10%) were more frequent, while cavitary forms were relatively less (8% *vs* 30%) in HIV-positive patients. Similar results have been reported from other studies in India[15-17] and various parts of the globe[4-10] (Table 4).

The presence of atypical and unusual lesions poses a clinical challenge. A negative tuberculin skin test may reflect the immunodeficiency status and does not rule out the presence of active tuberculosis. Sputum culture and blood culture may aid in the diagnosis in difficult cases. Mycobacteremia may be an uncommon event in immunocompetent individuals but an important cause of PUO in HIV infected patients as the CD4 declines. Ramachandran *et al* have reported a 10% positivity rate in isolating TB bacilli by blood culture in patients with CD4 below 100 cells / mm^3.[18] The diagnosis of TB in HIV positive persons, therefore, requires a high index of suspicion and a combination of clinical, radiographic and bacteriologic investigations. While there could be a variety of infectious and non-infectious causes for an abnormal chest radiograph, a normal radiograph does not rule out tuberculosis. Efforts should be made to develop a clinical diagnostic algorithm to diagnose TB, which could be used in resource - constrained settings.

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